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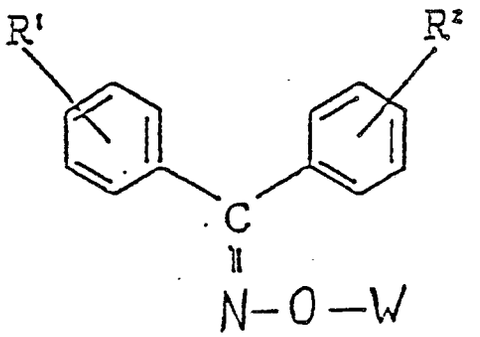
(54) Diphenyl-methane derivative, pharmaceutical composition and use.

(57) A new diphenyl-methane derivative is useful to inhibit agglomeration of blood and is defined by the formula,

including a diphenylethylene derivative and a benzophenone oxime ether derivative.



(I)

in which R1 and R2 each are hydrogen, hydroxyl or a lower alkoxy,
W is -CH2-CO-CH2-COOR13, R13 being hydrogen or a lower alkyl, -CH2-C(=NOR14)-CH2-COOR15, R15 being hydrogen or a lower alkyl, R14 being a lower alkyl, -CH(CN)-(CH2)q-COOR16, R16 being hydrogen or a lower alkyl, q being an integer of 1 to 3, or -(CH2)p-Z, Z being -SH, -SCN or a monovalent group derived from a five- or six-membered ring which may be substituted by a ring having one or more sulfur atoms in the ring, p being 1 or 2.

A pharmaceutical composition containing compounds of formula (I) or their pharmaceutically acceptable salts as active ingredients, and the use of compounds of formula (I) or their pharmaceutically acceptable salts in the preparation of a medicament for treatment of diseases caused by blood stream disorders are also disclosed.

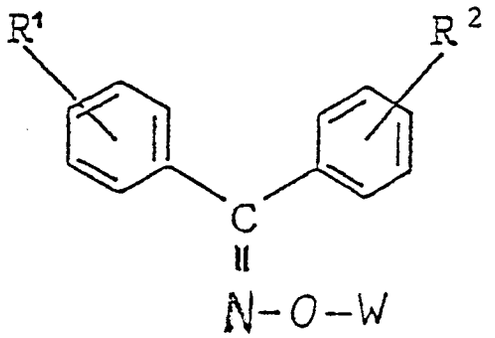
Diphenyl-Methane Derivative, Pharmaceutical Composition and Use

The invention relates to a diphenyl-methane derivative, a process for preparing the same and the pharmaceutical use thereof. In particular, it relates to a diphenylethylene derivative and a benzophenone oxime ether derivative.

The most serious diseases for mankind at present include acute vascular diseases such as myocardial infarction, cerebral apoplexy, cerebral thrombosis, cerebral infarction, pulmonary embolus, deep phlebothrombosis and peripheral arteriothrombosis.

Recently antiplatelet agents have attracted public attention and been clinically employed for treating these diseases. However their application has been only lately realized. Thus it is expected to develop better drugs in future.

The invention provides a diphenyl-methane derivative having the formula (XX) and a phamacologically acceptable salt thereof:



(I)

in which R1 and R2 each are hydrogen, hydroxyl or a lower alkoxy,

W is -CH2-CO-CH2-COOR13, R13 being hydrogen or a lower alkyl, -CH2-C(=NOR14)-CH2-COOR15, R15 being hydrogen or a lower alkyl, R14 being a lower alkyl, -CH(CN)-(CH2)q-COOR16, R16 being hydrogen or a lower alkyl, q being an integer of 1 to 3, or -(CH2)p-Z, Z being -SH, -SCN or a monovalent group derived from a five- or six-membered ring which may be substituted by a ring having one or more sulfur atoms in the ring, p being 1 or 2.

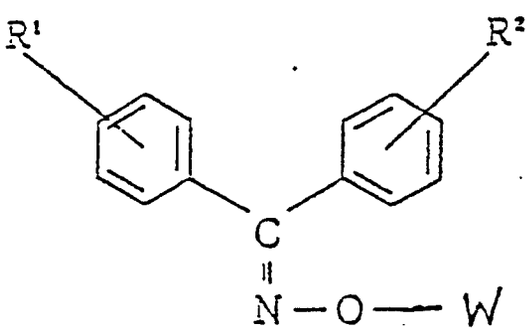
In addition, the invention provides a plurality of processes for preparing the above defined diphenyl-methane derivative. Each process is explained below in detail.

Moreover the invention provides a pharmaceutical composition which comprises a a pharmacologically effective amount of the diphenyl-methane derivative as defined above or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

In this connection, the invention provides a method of treating a disease caused by the blood stream disorder with administration of the diphenyl-methane derivative as defined above or a pharmacologically acceptable salt thereof.

The invention compound will be explained in more detail in line with the above shown embodiments.

The aimed compound of the present invention is a substituted benzophenone oxime ether derivative of the general formula (I) or a pharmaceutically acceptable salt thereof:

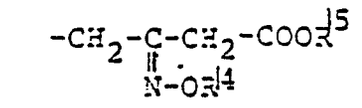


(I)

wherein R^1 and R^2 may be the same or different from each other and each represents a hydrogen atom or a lower alkoxy group; and

W represents a group of the formula $-CH_2-\underset{\underset{O}{\|}}{C}-CH_2-COOR^{13}$

(wherein R13 is a hydrogen atom or a lower alkyl group), a group of the formula



(wherein R^{15} represents a hydrogen atom or a lower alkyl group; and R^{14} represents a lower alkyl group), a group of the formula $-\underset{\underset{CN}{|}}{CH}-(CH_2)_q-COOR^{15}$

(wherein R^{15} represents a hydrogen atom or a lower alkly group; and q is an integer of 1 to 3) or a group of the formula $-(CH_2)_p-Z$ (wherein Z represents a group of the formula -SH, a group of the formula -SCN or a monovalent group derived from a five- or six-membered ring optionally substituted by a ring having one or more sulfur atoms in the ring; and p is an integer of 1 or 2).

In the above definition, a lower alkyl group as mentioned with regard to R^{13}, R^{14}, R^{15} and R^{16} includes straight-chain or branched alkyl groups carrying one to six carbon atoms, e.g., methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups. An alkoxy group as mentioned with regard to R^1 and R^2 includes any lower alkoxy group derived from the lower alkyl groups as cited above. Among these groups, methyl and ethyl groups are the most desirable lower alkyl groups while a methoxy group is the most desirable lower alkoxy group.

A monovalent group derived from a five- or six-membered ring optionally substituted by a ring containing one or more sulfur atoms in the ring as mentioned with regard to Z of the compound (XI) of the invention includes, for example, 1-pyrrolyl, 1-(1,2,3,4-tetrazolyl), 1-pyrrolidinyl, 1,3-dithianyl and 3-allylmercapto-1,2,4-triazolyl groups.

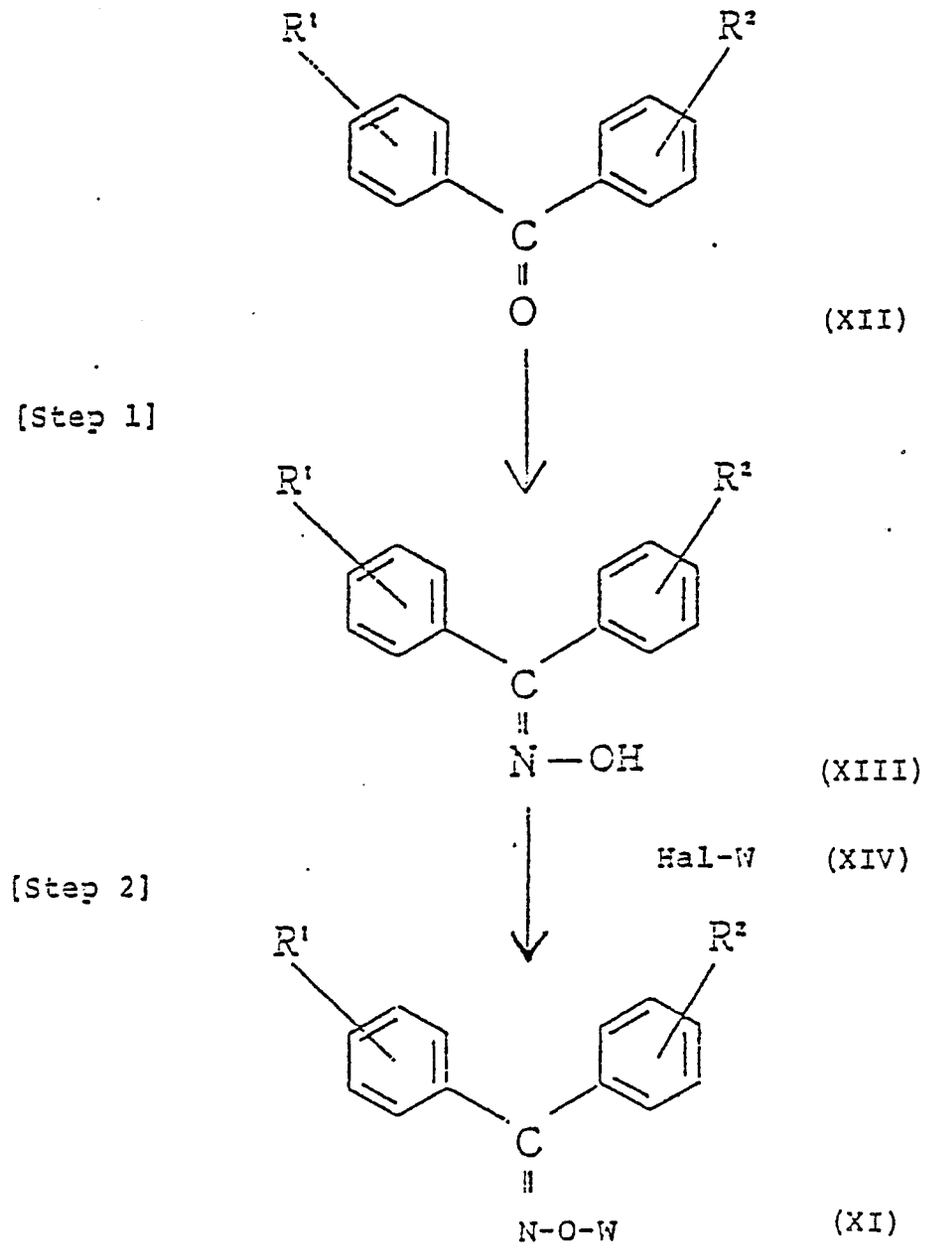
A pharmaceutically acceptable salt of the aimed compound of the formula (XI) in which R^{13}, R^{15} and/or R^{16} are hydrogen atoms includes metal salts such as Na, K, Ca and Mg salts.

Further some of the aimed compounds can be converted into acid addition salts by reacting the same with a pharmaceutically acceptable inorganic or organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic and sulfuric acids. Examples of such organic acids are maleic, fumaric, succinic, acetic, malonic, citric, benzoic, oxalic and methane-sulfonic acid.

Process for Preparation

There may be various processes for preparing the compound (I) of the invention. Typical examples thereof are as follows.

Preparation process 1



wherein R^1, R^2 and W are as defined above; and Hal represents a halogen atom.

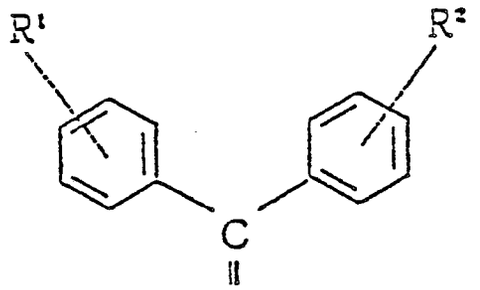
Namely, a benzophenone compound of the formula (XII) is reacted with a hydroxylamine to give a benzophenone oxime of the formula (XIII) (Step 1). Then the compound (XIII) is condensed with a halide of the formula (XIV) to give the aimed compound (XV) (Step 2). The obtained product may be converted into a pharmaceutically acceptable salt in a conventional manner, if required.

Step 1 may be usually carried out at a temperature of approximately 0 to 200° C, preferably at room temperature to 100° C with the use of a solvent such as methanol, ethanol, propanol, benzene, toluene or water.

Step 2 may be usually carried out at a temperature of approximately 0 to 100° C with the use of a solvent such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), methanol, ethanol, propanol, benzene or toluene. The reaction may be carried out in the presence of a base such as sodium hydride (NaH), triethylamine, dimethylaniline, potassium hydroxide, methoxysodium (NaOMe), ethoxysodium (NaOEt) or tert-buthoxypotassium to give a preferable result.

Preparation process 2

Aimed compound of the formula (XI) wherein R^{13}, R^{15} and R^{16} in W are hydrogen atoms
An ester of the formula:

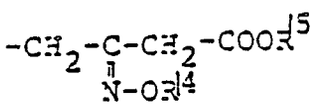


(XV)

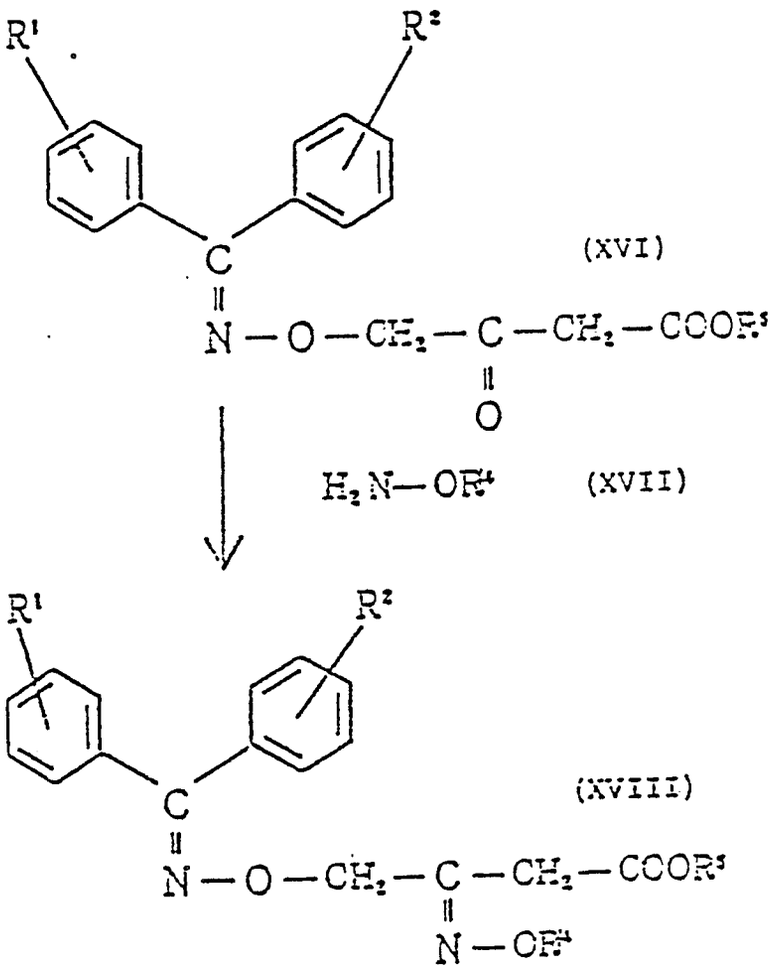
wherein W′ has the same meaning as that of W in the general formula (I) except that R^{13}, R^{15}, and R^{16} are hydrogen atoms, i.e., lower alkyl groups, is hydrolyzed in a conventional manner, for example, with an alkali such as caustic soda to give the aimed compound.

Preparation process 3

Aimed compound of the general formula (I) wherein W represents a group of the formula



represents a lower alkyl group; and R^{15} represents a hydrogen atom or a lower alkyl group)



wherein R^1, R^2, R^{14} and R^{15} are as defined above.

Namely, a compound of the general formula (XVI) is reacted with an amine of the general formula (XVII) to give a compound (XVIII) which is one of the aimed compounds. This reaction may be preferably carried out at a temperature of approximately - 20 to 200 °C in a solvent such as methanol, ethanol, propanol, benzene, toluene or water.

In order to further illustrate the present invention, and not by way of limitation, typical examples of the compound of the present invention will be given. Each compound will be shown in free form.

4,4′-dimethoxybenzophenone 0-(3-methoxycarbonyl-2-oxopropyl)oxime,
4,4′-dimethoxybenzophenone 0-(3-ethoxycarbonyl-2-oxopropyl)oxime,
4,4′-dimethoxybenzophenone 0-(3-methoxycarbonyl-2-methoxyiminopropyl)oxime,
4,4′-dimethoxybenzophenone 0-(3-ethoxycarbonyl-2-methoxyiminopropyl)oxime,
4,4′-dimethoxybenzophenone 0-(3-carboxy-2-methoxyiminopropyl)oxime,
4,4′-dimethoxybenzophenone 0-(1-cyano-3-methoxy carbonylpropyl)oxime,
4,4′-dimethoxybenzophenone 0-(1-cyano-3-ethoxycarbonylpropyl)oxime,
4,4′-dimethoxybenzophenone 0-(1-cyano-3-carboxypropyl)oxime,
4,4′-dimethoxybenzophenone 0-(1-cyano-4-methoxycarbonylbutyl)oxime,
4,4′-dimethoxybenzophenone 0-(1-cyano-4-carboxybutyl)oxime,
4,4′-dimethoxybenzophenone 0-{2-(3-allylmercapto-1,2,4-triazolyl)]ethyl}oxime,
4,4′-dimethoxybenzophenone 0-{2-[1-(1,2,3,4-tetrazolyl)]ethyl}oxime,
4,4′-dimethoxybenzophenone 0-{2-[2-(1,3-dithianyl)]ethyl}oxime,
4,4′-dimethoxybenzophenone 0-[2-(1-pyrrolidinyl)ethyl]oxime,
4,4′-dimethoxybenzophenone 0-(2-thiocyanatoethyl)oxime,
4,4′-dimethoxybenzophenone 0-(2-mercaptoethyl)oxime,
4,4′-dimethoxybenzophenone 0-[2-(1-pyrrolyl)ethyl]oxime,
4,4′-diethoxybenzophenone 0-(3-ethoxycarbonyl-2-oxopropyl)oxime,
4,4′-diethoxybenzophenone 0-(3-ethoxycarbonyl-2-methoxyiminopropyl)oxime,

4,4′-diethoxybenzophenone 0-(3-carboxy-2-methoxyiminopropyl)oxime,
4,4′-diethoxybenzophenone 0-(1-cyano-3-ethoxycarbonylpropyl)oxime,
4,4′-diethoxybenzophenone 0-(1-cyano-3-carboxypropyl)oxime,
methoxybenzophenone 0-(3-ethoxycarbonyl-2-oxopropyl)oxime,
4-methoxybenzophenone 0-(3-ethoxycarbonyl-2-methoxyiminopropyl)oxime,
4-methoxybenzophenone 0-(3-carboxy-2-methoxyiminopropyl)oxime,
4-methoxybenzophenone 0-(1-cyano-3-ethoxycarbonylpropyl)oxime, and
4-methoxybenzophenone 0-(1-cyano-3-carboxypropyl)oxime.

The diphenyl-methane derivative of the invention, both diphenylene derivative and benzophenone oxime ether derivative, exhibits an excellent effect in the pharmacological point of view. It effectively inhibits the aggulutination of platelets and eventually is useful for a remedy of an antiplatelet and antithrombotic agent. In particular, it is useful for treating and/or preventing cerebrovascular diseases such as transient ischemic attack (TIA), cerebral infarction (thrombus and embolus) and cerebral arteriosclerosis; postoperative thrombus, embolus and blood stream disorders accompanying vascular operation and extracorporeal circulation; chronic arterial obstructions such as Buerger's disease, obstructive arteriosclerosis, peripheral arteriosclerosis, SLE and Raynaud's disease; and ischemic cardial diseases such as stenocardia and myocardial infarction. It is further useful for preventing recurrence of these diseases and for improving prognosis thereof.

The effect of the invention product will be supported by the below given pharmacological tests, first about the diphenylethylene derivative.

Test Example

1. Effect of inhibiting aggulutination of platelets (in vitro)

The blood was collected from a human cubital vein in such a manner as to contain a 3.8% solution of sodium citrate in an amount 1.10 time by volume as much as the blood. Then platelet-rich plasma (PRP) was prepared therefrom according to the method reported by Packham et al. (cf. Packham, M.A., et al, J. Exp. Med., 126, 171 - 189 (1967)). To 0.2 ml of the obtained PRP, 25µl portions of solutions of each compound of the present invention (A to E) at various concentrations were added and incubated at 37° C for three minutes. Then the aggultination of platelets was induced with arachidonic acid, collagen, ADP and PAF. The aggulutination of platelets was evaluated according to the method reported by Mustard et al. (cf. Mustard, J.F., et al., J. Lab. Clin. Med., 64, 548 - 559 (1964) with the use of an aggregometer available from Schenko or Niko Bioscience Co. In other words, this test is carried out to examine the effect on platelet aggregation (in vitro).

When the compound of the present invention is used as an antiplatelet and antithrombotic agent, it may be orally or parenterally, for example, intramuscularly, subcutaneously or intravenously administered. The dose thereof may vary depending on, for example, the disease, the condition and the age of each patient. Unless particularly limited, it may be administered in a dose of 0.1 to 300 mg, preferably 0.1 to 60 mg, particularly preferably 0.3 to 30 mg, further particularly preferably 0.6 to 10 mg to an adult per day.

The compound of the present invention may be formulated into, for example, tablets, granules, powders, capsules, injections or suppositories in conventional manners known in the art.

When it is to be formulated into solid preparations for oral administration, excipients and, if required, other additives such as binders, disintegrants, lubricants, colorants and corrigents are added to the base and the obtained mixture is then formulated into, for example, tablets, coated tablets, granules, powders or capsules in conventional manners.

Examples of the excipients are lactose, corn starch, white sugar, glucose, sorbitol and crystalline cellulose. Examples of the binders are polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrants are starch, agar, powdery gelatin, crystalline cellulose, calcium carbonate, calcium hydrogencarbonate, calcium citrate, dextrin and pectin. Examples of the lubricants are magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. Examples of the colorants are those approved as additives for drugs. Examples of the corrigents are cocoa powder, methol, aromatic acids, peppermint oil, Borneo camphor and cinnamon powder. These tablets and granules may be, as a matter of course, coated with, for example sugar or gelatin if required.

When an injection is to be prepared, various additives such as pH adjustors, buffers, stabilizers and

preservatives are added to the base and the obtained mixture is formulated into an injection for subcutaneous, intramuscular or intravenous administration.

To further illustrate the present invention, and not by way of limitation, the following Examples will be given.

Example 1: 4,4′-dimethoxybenzophenone-O-(3-ethoxycarbonyl-2-oxopropyl)oxime

(1) Synthesis of 4,4′-dimethoxybenzophenone oxime

242 g (1 mole) of 4,4′-dimethoxybenzophenone was suspended in 2,000 ml of ethanol and 210 g (3 mole) of hydroxylamine hydrochloride and 300 ml (3 mole) of a 10 N aqueous solution of NaOH were added thereto. Then the obtained mixture was heated under reflux. After two or three hours, the ethanol was distilled off in vacuo and then a saline solution was added thereto followed by extracting with chloroform. The chloroform phase was washed with water and dried over magnesium sulfate. After distilling the chloroform off, the residue was recrystallized from ethanol. Thus 240 g of the title compound was obtained in the form of colorless needles. m.p.: 131 to 132° C.
NMR ($CDCl_3$)δ: 9.60 (b-s, 1H), 7.50 (m, 8H), 3.83 (s, 3H) 3.80 (s, 3H).

(2) Synthesis of 4,4′-dimethoxybenzophenone O-(3-ethoxycarbonyl-2-oxopropyl)oxime

2.57 g (0.01 mol) of the 4,4′-dimethoxybenzophenone oxime as obtained in (1) was dissolved in 5 ml of dimethylformamide and 1.2 g of potassium tert-butoxide was added thereto under ice cooling. The resulting mixture was stirred for ten minutes. Then 1.8 g of ethyl 4-chloroacetoacetate was added thereto and the obtained mixture was stirred at room temperature. After two hours, the reaction mixture was poured into diluted hydrochloric acid and extracted with ethanol. The crude product thus obtained was purified by silica gel chromatography to give 3.1 g of the title compound.

o NMR ($CDCl_3$) δ :

6.7–7.4 (8H), 4.6 (2H) 3.9–4.2 (2H)

3.8 (6H) 3.5 (2H), 1.2 (3H)

Example 2: 4,4′-Dimethoxybenzophenone O-(3-ethoxycarbonyl-2-methoxyiminopropyl)oxime

3.85 g of the 4,4′-dimethoxybenzophenone O-(3-ethoxycarbonyl-2-oxopropyl)oxime as obtained in Example 1 was dissolved in 5 ml of pyridine and 1 g of methoxylamine hydrochloride was added thereto. Then the obtained mixture was stirred at room temperature. After two hours, the reaction mixture was poured into ethyl acetate, washed with diluted hydrochloric acid and then with a saturated saline solution and purified by silica gel chromatography. Thus 4 g of the title compound was obtained in the form of a colorless oily product.

o NMR ($CDCl_3$) δ :

6.7—7.4 (8H), 5.0, 4.7 (2H),

3.8—4.2 (2H) 3.8 (9H) 3.3, 3.4 (2H)

1.0—1.2 (3H)

Example 3: 4,4′-Dimethoxybenzophenone O-(3-carboxy-2-methoxyiminopropyl)oxime

4.14 g of the 4,4′-dimethoxybenzophenone O-(3-ethoxycarbonyl-2-methoxyiminopropyl)oxime as obtained in Example 2 was dissolved in 20 ml of methanol and 3 ml of a 5 N aqueous solution of caustic soda was added thereto. The obtained mixture was stirred at room temperature for five hours. After the completion of the reaction, the reaction mixture was acidified with diluted hydrochloric acid and extracted with ethyl acetate. Thus 3.8 g of the title compound was obtained in the form of a colorless oily product.

o NMR ($CDCl_3$) δ : 9.50 (1H), 6.8—7.5 (8H),

5.0, 6.8 (2H), 3.8—3.9 (9H), 3.5,

3.3 (2H)

Example 4: 4,4′-Dimethoxybenzophenone O-(1-cyano-3-ethoxycarbonylpropyl)oxime

The procedure of Example 1 was followed except that the ethyl 4-chloroacetoacetate was replaced by 2.2 g of ethyl 4-bromo-4-cyanobutyrate. Thus 3.6 g of the title compound having the following properties was obtained.

o NMR ($CDCl_3$) δ : 6.8—7.5 (8H), 5.0 (1H),

4.0—4.3 (2H), 3.8 (6H),

2.2—2.6 (4H), 1.2 (3H)

Example 5: 4,4′-Dimethoxybenzophenone O-(1-cyano-3-carboxypropyl)oxime

3.96 g of the 4,4′-dimethoxybenzophenone O-(1-cyano-3-ethoxycarbonylpropyl)oxime was dissolved in 20 ml of dioxane and 3 ml of a 5 N aqueous solution of caustic soda was added thereto. Then the mixture was allowed to react at 60° C for five hours. After the completion of the reaction, the reaction mixture was acidified and extracted with ethyl acetate. Thus 3.6 g of the title compound was obtained in the form of a colorless oily product.

o NMR ($CDCl_3$) δ :

6.7—7.5 (8H), 5.0 (1H) 3.8 (6H)

2.1—2.7 (4H)

Example 6: 4,4′-Dimethoxybenzophenone O-(1-cyano-4-methoxycarbonylbutyl)oxime

The procedure of Example 1 was followed except that the ethyl 4-chloroacetoacetate was replaced by 2.2 g of methyl 5-bromo-5-cyanopentanoate. Thus 3.7 g of the title compound of the following properties was obtained.

o NMR ($CDCl_3$) δ : 6.8—7.6 (8H), 4.9 (1H),

3.8 (6H), 3.6 (3H), 2.4 (2H),

1.6—2.2 (4H)

Example 7: 4,4′-Dimethoxybenzophenone O-(1-cyano-4-carboxybutyl)oxime

According to the procedure of Example 5, the title compound of the following properties was obtained.

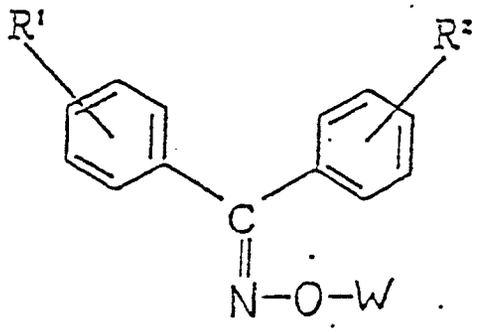
o NMR ($CDCl_3$) δ : 6.7—7.5 (8H), 4.9 (1H),

3.8 (6H), 2.4 (2H),

1.5—2.2 (4H)

Claims

(1) A diphenyl-methane derivative having the formula (I) and a phamacologically acceptable salt thereof:



(I)

in which R1 and R2 each are hydrogen, hydroxyl or a lower alkoxy,
W is -CH2-CO-CH2-COOR13, R13 being hydrogen or a lower alkyl, -CH2-C(=NOR14)-CH2-COOR15, R15

being hydrogen or a lower alkyl, R14 being a lower alkyl, -CH(CN)-(CH2)q-COOR16, R16 being hydrogen or a lower alkyl, q being an integer of 1 to 3, or -(CH2)p-Z, Z being -SH, -SCN or a monovalent group derived from a five- or six-membered ring which may be substituted by a ring having one or more sulfur atoms in the ring, p being 1 or 2.

(2) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are lower alkoxy groups and W is a group of the formula $-CH_2-\overset{\overset{O}{\|}}{C}-CH_2-COOR^{13}$ (wherein R^{13} represents a hydrogen atom or a lower alkyl group), and a pharmaceutically acceptable salt thereof.

(3) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are lower alkoxy groups and W is a group of the formula

$$-CH_2-\overset{\overset{N-OR^{14}}{|}}{\underset{\|}{C}}-CH_2-COOR^{15}$$

(wherein R^{15} represents a hydrogen atom or a lower alkyl group; and R^{14} represents a lower alkyl group), and a pharmaceutically acceptable salt thereof.

(4) A substituted benzophenone oxime ether derivative as set for th in Claim 1 wherein both of R^1 and R^2 are lower alkoxy groups and W is a group of the formula $-\underset{\underset{CN}{|}}{CH}-(CH_2)_q-COOR^{16}$ wherein R^{16} represents a hydrogen atom or a lower alkyl group; and q is an integer of 1 to 3), and a pharmaceutically acceptable salt thereof.

(5) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are lower alkoxy groups and W is a group of the formula $-(CH_2)_p-Z$ (wherein Z represents a group of the formula -SCN or a monovalent group derived from a five-or six-membered ring optionally substituted by a ring having one or more sulfur atoms in the ring; and p is an integer of 1 or 2), and a pharmaceutically acceptable salt thereof.

(6) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are methoxy groups and W is a group of the formula

$$-CH_2-\overset{\overset{N-OCH_3}{|}}{\underset{\|}{C}}-CH_2-COOR^{15}$$

(wherein R^{15} represents a hydrogen atom or a lower alkyl group), and a pharmaceutically acceptable salt thereof.

(7) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are methoxy groups and W is a group of the formula

$$-CH_2-\overset{\overset{N-OCH_3}{|}}{\underset{\|}{C}}-CH_2-COOH,$$

and a pharmaceutically acceptable salt thereof.

(8) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are methoxy groups and W is a group of the formula $-\underset{\underset{CN}{|}}{CH}-(CH_2)_q-COOR^{16}$ (wherein R^{16} represents a hydrogen atom or a lower alkyl group; and q is an integer of 1 to 3), and a pharmaceutically acceptable salt thereof.

(9) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are methoxy groups and W is a group of the formula $-\underset{\underset{CN}{|}}{CH}-(CH_2)_2-COOC_2H_5$, and a pharmaceutically acceptable thereof.

(10) A substituted benzophenone oxime ether derivative as set forth in Claim 1 wherein both of R^1 and R^2 are methoxy groups and W is a group of the formula - $\underset{\underset{CN}{|}}{CH}$ -$(CH_2)_2$-COOH,

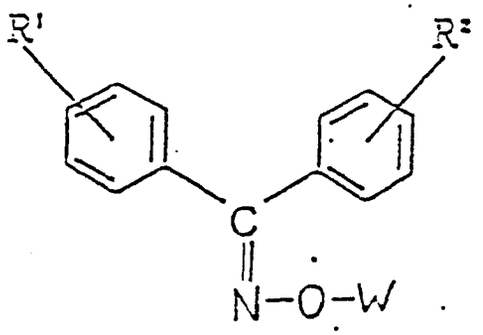
and a pahrmaceutically acceptable salt thereof.

(11) A pharmaceutical composition which comprises a pharmacologically effective amount of the diphenylmethane derivative as defined in Claim 1 or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

(12) Use of the compounds of any of claims 1 to 10 in the preparation of a medicament for the treatment of diseases caused by blood stream disorders.

Claims for the following Contracting States: AT, ES, GR.

1. A process for preparing a compound of formula (I)



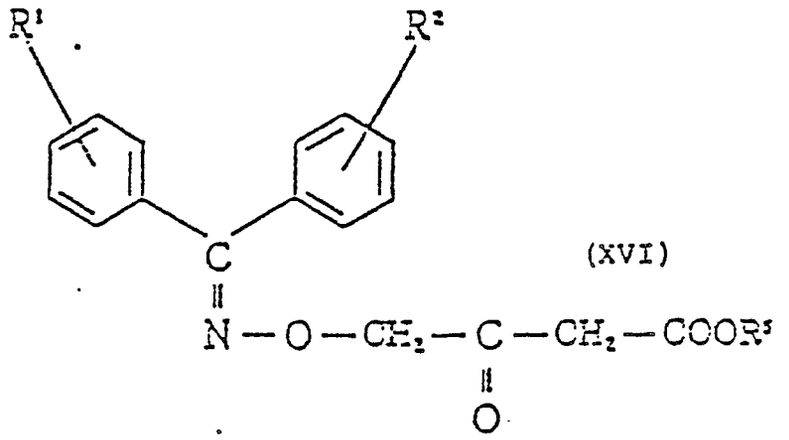
(I)

in which R1 and R2 each are hydrogen, hydroxyl or a lower alkoxy,
W is -CH2-CO-CH2-COOR13, R13 being hydrogen or a lower alkyl, -CH2-C(=NOR14)-CH2-COOR15, R15 being hydrogen or a lower alkyl, R14 being a lower alkyl, -CH(CN)-$(CH2)_q$-COOR16, R16 being hydrogen or a lower alkyl, q being an integer of 1 to 3, or -(CH2)p-Z, Z being -SH, -SCN or a monovalent group derived from a five- or six-membered ring which may be substituted by a ring having one or more sulfur atoms in the ring, p being 1 or 2. where R13, R15, and R16 are hydrogen, R14 is lower alkyl and q is an integer of 1 to 3 or a pharmaceutically acceptable salt thereof which comprises hydrolyzing the above compounds of formula (I) where R13, R15 and R16 are lower alkyl and q and R14 are as defined above, and if necessary converting the product to a pharmaceutically acceptable salt.

2. Process for preparing a compound of the general formula (I) wherein R1 and R2 are as defined in claim 1 where W represents a group of the formula

$$-CH_2-\underset{\underset{N-OR^4}{|}}{C}-CH_2-COOR^5$$

where R14 represents a lower alkyl group; and R15 represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof which comprises reacting a compound of formula (XVI):



(XVI)

where R15 is as defined above with a compound of formula (XVII):

$H_2N\text{-}OR^4$ (XVII)

where R14 is as defined above and if necessary converting the product to a pharmaceutically acceptable salt.

3. Use of the compounds of formula (I) of claim 1 or the pharmaceutically acceptable salts thereof produced in any of the preceding claims in the preparation of a medicament for treatment of diseases caused by blood stream disorders.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 11 4183

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	FR-A-2 385 691 (I.C.I.) * Claims * -----	1	C 07 C 131/00 C 07 D 207/325 C 07 D 249/12 C 07 D 257/04 C 07 D 295/08 C 07 D 339/08 C 07 C 149/18 C 07 C 161/02 A 61 K 31/15
			TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 C 131/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12-09-1989	HELPS I.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
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